


INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WPP86390	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB 03/04836	International filing date (day/month/year) 10.11.2003	Priority date (day/month/year) 11.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/72		
Applicant MEDPHARM LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 11.06.2004	Date of completion of this report 30.05.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Sindel, U Telephone No. +49 89 2399-7064



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 03/04836**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-31 as originally filed

Claims, Numbers

1-29 received on 27.04.2004 with letter of 23.04.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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International application No. PCT/GB 03/04836

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-29
	No: Claims	-
Inventive step (IS)	Yes: Claims	1-29
	No: Claims	-
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	-

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/04836

Item V

- 1 Reference is made to the following documents:

D1: US 2002/010318 A1 (WRIGHT CLIFFORD D ET AL) 24 January 2002
D2: US 2002/106368 A1 (WOODS CATHERINE M ET AL) 8 August 2002

- 2 Novelty and Inventive Step

The subject-matter of claims 1-29 seems to be new in the sense of Article 33(2) PCT and involves an inventive step in the sense of Article 33(3) PCT in view of the present prior art.

The problem to be solved is the provision of an improved stable dry powder formulation for use in metered dose inhalers comprising proteins or peptides in presence of hydrofluoroalkanes (HFA).

The solution provided is a preparation comprising a combination of a disaccharide and polyvinyl alcohol (PVA) as stabilizers.

Closest prior art is D1 disclosing a powder composition suitable for inhalation via e.g. a metered dose inhaler (MDI) comprising secretory leukocyte protease inhibitor (SLPI) protein as active agent and carbohydrates like mannitol, sucrose, trehalose as stabilizers (see abstract, paragraph [0126] and claims 1, 7). PVA is part of a list of usable stabilizers (see paragraph [0075]). There is no hint given that a combination of a disaccharide with polyvinyl alcohol would improve stability of proteins and peptides in presence of hydrofluoroalkanes (HFA).

Hence, the subject-matter of present claims 1-29 is new and seems to involve an inventive step.

- 3 Industrial applicability

The subject matter of claims 1-29 is industrially applicable in the sense of Article 33(4) PCT.

CLAIMS:

1. A formulation of a therapeutic substance suitable for delivery to a patient by a metered dose inhalation device, the formulation comprising a substantially dry powder preparation of the substance in association with a stabilising amount of a glycoside and a polyhydroxylated polyalkene in combination with one or more propellants therefor, wherein the therapeutic substance is selected from peptides and proteins.
2. A formulation according to claim 1, further comprising a cosolvent for said substance.
3. A formulation according to any preceeding claim, wherein the therapeutic substance is selected from antibodies, interferons, enzymes, hormones, euprolide acetate, CFTR, and α 1-antitrypsin.
4. A formulation according to claim 3, wherein the therapeutic substance is a hormone selected from insulin, LHRH, granulocyte-colony stimulating factor, calcitonin, heparin, human growth hormone, and parathyroid hormone.
5. A formulation according to claim 1, wherein the substance is dnase I.
6. A formulation according to any preceding claim, which is non-immunogenic.
7. A formulation according to any preceding claim which is capable of being stored at room temperature without losing more than 50% biological activity of the therapeutic substance after two months.
8. A formulation according to any preceding claim, wherein the glycoside comprises at least one oligosaccharide.
9. A formulation according to claim 8, wherein the glycoside comprises at least one disaccharide.

10. A formulation according to claim 9, wherein the disaccharide is selected from trehalose, mannitol, sucrose, and mixtures thereof.
11. A formulation according to any preceding claim, wherein the glycoside constitutes between about 30% and 400% by weight of the therapeutic substance.
12. A formulation according to any preceding claim, wherein the propellant is alkane based.
13. A formulation according to claim 12, wherein the propellant is at least one haloalkane.
14. A formulation according to claim 13, wherein the propellant is selected from HFA-134a and HFA-227.
15. A formulation according to any preceding claim, wherein at least one polyhydroxylated polyalkene has the general structure
- $$-(\text{CH}_2-\text{CHOR})_n-$$
- where R is the same or different from one monomeric unit to the next, and is hydrogen, lower alkyl, lower alkenyl, lower alkanoyl, lower alenoyl or is a bridging group between adjacent monomers.
16. A formulation according to claim 15, wherein, when R is not hydrogen, the number of carbon atoms, excluding any $-\text{CO}-$ group, is between 1 and 6, inclusive.
17. A formulation according to claim 15 or 16, wherein the polyhydroxylated polyalkene is selected from polyvinylalcohol, polyvinylacetate, polyvinyl alcohol-co-vinyl acetate, poly(vinyl butyral), poly(vinyl alcohol-co-ethylene), and mixtures thereof.
18. A formulation according to claim 17, wherein the polyhydroxylated polyalkene is PVA.

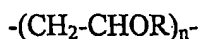
19. A formulation according to claim 17 or 18, wherein the PVA a hydrolysate of PVAc, the level of hydrolysis being between 40% and 100%.
20. A formulation according to claim 17 or 18, wherein the PVA a hydrolysate of PVAc, the level of hydrolysis being between 50 and 90%.
21. A formulation according to any of claims 17 to 20, wherein the PVA has a molecular weight of between about 9 kDa and 50 kDa.
22. A formulation according to any preceding claim, wherein the polyhydroxylated polyalkenes are present in an amount of from about 5% to about 200% by weight of the therapeutic substance.
23. A formulation according to claim 22, wherein the polyhydroxylated polyalkene is present between about 10% and about 50% by weight of the substance.
24. A method for the preparation of a formulation as defined in any preceding claim, comprising blending the therapeutic agent with the glycoside and polyhydroxylated polyalkene substances in an aqueous vehicle, drying the resulting blend to a powder, and then formulating with propellant.
25. A method according to claim 24, wherein the aqueous vehicle is selected from saline, a suitable buffer, and deionised water.
26. A method according to claim 24 or 25, which comprises spray—drying the blend.
27. A powdered formulation of a therapeutic agent, a glycoside and a polyhydroxylated polyalkene, as defined in any of claims 1 to 23, which is suitable for incorporation with a haloalkane propellant for dispensing from a metered dose inhaler.
28. A powdered formulation according to claim 27, wherein the powder particles have an aerodynamic diameter of between about 1 μm and 50 μm .

29. A metered dose inhalation device provided with a reservoir comprising a formulation according to any of claims 1 to 23.

CLAIMS:

1. A formulation of a therapeutic substance suitable for delivery to a patient by a metered dose inhalation device, the formulation comprising a substantially dry powder preparation of the substance in association with a stabilising amount of a glycoside and a polyhydroxylated polyalkene in combination with one or more propellants therefor.
2. A formulation according to claim 1, further comprising a cosolvent for said substance.
3. A formulation according to claim 1 or 2, wherein the therapeutic substance is selected from peptides and proteins.
4. A formulation according to claim 3, wherein the substance is selected from antibodies, interferons, enzymes, hormones, euprolide acetate, CFTR, and α 1-antitrypsin.
5. A formulation according to claim 4, wherein the substance is a hormone selected from insulin, LHRH, granulocyte-colony stimulating factor, calcitonin, heparin, human growth hormone, and parathyroid hormone.
6. A formulation according to claim 3, wherein the substance is dnase I.
7. A formulation according to any preceding claim, which is non-immunogenic.
8. A formulation according to any preceding claim which is capable of being stored at room temperature without losing more than 50% biological activity of the therapeutic substance after two months.
9. A formulation according to any preceding claim, wherein the glycoside comprises at least one oligosaccharide.
10. A formulation according to claim 9, wherein the glycoside comprises at least one disaccharide.
11. A formulation according to claim 10, wherein the disaccharide is selected from trehalose, mannitol, sucrose, and mixtures thereof.

12. A formulation according to any preceding claim, wherein the glycoside constitutes between about 30% and 400% by weight of the therapeutic substance.
13. A formulation according to any preceding claim, wherein the propellant is alkane based.
14. A formulation according to claim 13, wherein the propellant is at least one haloalkane.
15. A formulation according to claim 14, wherein the propellant is selected from HFA-134a and HFA-227.
16. A formulation according to any preceding claim, wherein at least one polyhydroxylated polyalkene has the general structure



where R is the same or different from one monomeric unit to the next, and is hydrogen, lower alkyl, lower alkenyl, lower alkanoyl, lower alenoyl or is a bridging group between adjacent monomers.

17. A formulation according to claim 16, wherein, when R is not hydrogen, the number of carbon atoms, excluding any $-\text{CO}-$ group, is between 1 and 6, inclusive.
18. A formulation according to claim 16 or 17, wherein the polyhydroxylated polyalkene is selected from polyvinylalcohol, polyvinylacetate, polyvinyl alcohol-co-vinyl acetate, poly(vinyl butyral), poly(vinyl alcohol-co-ethylene), and mixtures thereof.
19. A formulation according to claim 18, wherein the polyhydroxylated polyalkene is PVA.
20. A formulation according to claim 18 or 19, wherein the PVA a hydrolysate of PVAc, the level of hydrolysis being between 40% and 100%.
21. A formulation according to claim 18 or 19, wherein the PVA a hydrolysate of PVAc, the level of hydrolysis being between 50 and 90%.

22. A formulation according to any of claims 18 to 21, wherein the PVA has a molecular weight of between about 9kDa and 50kDa.
23. A formulation according to any preceding claim, wherein the polyhydroxylated polyalkenes are present in an amount of from about 5% to about 200% by weight of the therapeutic substance.
24. A formulation according to claim 23, wherein the polyhydroxylated polyalkene is present between about 10% and about 50% by weight of the substance.
25. A method for the preparation of a formulation as defined in any preceding claim, comprising blending the therapeutic agent with the glycoside and polyhydroxylated polyalkene substances in an aqueous vehicle, drying the resulting blend to a powder, and then formulating with propellant.
26. A method according to claim 25, wherein the aqueous vehicle is selected from saline, a suitable buffer, and deionised water.
27. A method according to claim 25 or 26, which comprises spray—drying the blend.
28. A powdered formulation of a therapeutic agent, a glycoside and a polyhydroxylated polyalkene, as defined in any of claims 1 to 24, which is suitable for incorporation with a haloalkane propellant for dispensing from a metered dose inhaler.
29. A powdered formulation according to claim 28, wherein the powder particles have an aerodynamic diameter of between about 1 μ m and 50 μ m.
30. A metered dose inhalation device provided with a reservoir comprising a formulation according to any of claims 1 to 24.